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"FORMULATION, DEVELOPMENT AND EVALUATION OF NANOPARTICULATE DRUG DELIVERY SYSTEM FOR ANTICANCER DRUG"

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1. Abstract of proposed work plan/ problem:

In recent years nanoparticulate drug delivery system has proved to be more efficacious and safe and created more importance in treatment of various diseases as compared with conventional drug delivery system. This is especially true in treatments like cancer chemotherapy where drug has to reach to specific cancer cells in sufficient amount with minimum effects on normal tissues or organs. Also many of the anticancer agents are having problems like less water solubility, pre-systemic metabolism, gastrointestinal instability, drug resistance (p-gp substrate) etc. which may affect its bioavailability. These problems can be solved in some extent by formulating lipid based nano drug delivery system like liposomes. But liposomes have some disadvantages viz. poor mechanical stability, susceptible for oxidation and hydrolysis, low entrapment efficiency, low solubility etc. While on other hand nanocochleates are devoid of these disadvantages. In last few years, the formulation of rifampicin, amphotericin B, paclitaxel (PTX), fisetin and quercetin nanocochleates was found to be promising and showed a good strategy to improve drugs bioavailability, efficacy and safety in various disease treatments especially in cancer chemotherapy. Based on the review of articles on nanocochleates we found that it's a need of hour to formulate and evaluate anticancer drug as nanocochleates. Anticancer drug-loaded nanocochleates will be prepared from liposomes by trapping or hydrogel method. Such prepared drug loaded nanocochleates will be optimized and evaluated for particle size, zeta potential, entrapment efficacy, PXRD, DSC, TEM, in-vitro drug release, in vivo pharmacokinetic study, in vitro anticancer cell line study and stability studies.

2. Introduction:

Nanoparticulates- A potential drug carriers

The challenges with use of large size materials in drug delivery, some of which include poor bioavailability, in vivo stability, solubility, intestinal absorption, sustained and targeted delivery to site of action, therapeutic effectiveness, generalized side effects, and plasma fluctuations of drugs.

To overcome these challenges several researches in nanodrug delivery have been designed through the development and fabrication of nanostructures. It has been proved that, nanostructures have the ability to protect drugs from the degradation in the gastrointestinal tract; the technology can allow target delivery of drugs to various areas of the body. The technology enables the delivery of drugs that are poorly water soluble and can provide means of bypassing the liver, thereby preventing the first pass metabolism. Nanotechnology increases oral bioavailability of drugs due to their specialized uptake mechanisms such as absorptive endocytosis and are able to remain in the blood circulation for a long time, releasing the incorporated drug in a controlled fashion, leading to less plasma fluctuations and minimized side-effects.

Nanosize nanostructures are able to penetrate tissues and are easily taken up by cells, allowing for efficient delivery of drugs to target sites of action. Uptake of nanostructures has been reported to be 15–250 times greater than that of microparticles in the 1–10 μm range. Nanotechnology improves performance and acceptability of dosage forms by increasing their effectiveness, safety, patient adherence, as well as ultimately reducing health care costs.

Various nanostructures, including liposomes, polymers, dendrimers, silicon or carbon materials, and magnetic nanoparticles, have been tested as carriers in drug delivery systems.

Lipid based delivery systems have attracted enormous attention by researchers to improve drug delivery. One of them, called liposome, is favorable due to its resemblance with the cell membrane. It possess various advantages such as provides selective passive targeting to tumor tissues, increases efficacy and therapeutic index of drug molecule, increases stability via encapsulation, reduces toxicity of the encapsulated agents, shows site avoidance effect, improves pharmacokinetic parameters of drug molecule (reduced elimination, increased circulation life times), imparts flexibility to couple with site specific ligands to achieve active

targeting, help to reduce exposure of sensitive tissues to toxic drugs, liposomes are biocompatible, completely biodegradable, non-toxic, flexible and non-immunogenic for systemic and non-systemic administrations.

Challenges in cancer chemotherapy

The aim of the ideal cancer chemotherapy is to deliver the correct amount of drug with desired controlled rate and for sufficiently long duration of time to the site of action (cancer cells), while prevent the normal cells to obtain the desired therapeutic response. In order to achieve this goal, drug delivery systems must hold sufficient amount of drug and root out the problems like drug resistance based on cellular or non-cellular mechanism, altered biodistribution, biotransformation as well as clearance of anticancer drugs from the body.

The delivery systems should meet the requirements like prolonged circulation (which can obtain by PEGylation), sufficient tumor accumulation (by considering EPR effect), uptake by tumor cells (by active targeting) and controlled drug release (by optimizing delivery system) with a profile matching the pharmacodynamics of the drug. By formulating nanocarrier based drug delivery system we can overcome above challenges in cancer chemotherapy.

Nanocochleates- A novel nanoparticulate drug delivery

Cochleates are elongated rolled microstructures that consist of a series of lipid bilayers formed as a result of condensation of small unilamellar negatively charged liposomes. These structures were first reported by Papahadjopoulos and Wilschut (Papahadjopoulos and Wilschut, 1979). Various formulation modifications with liposomes allowed the development of a new class of the drug vehicles called “COCHLEATE.” Cochleates are solid particulates which are made up of large continuous, lipid bi-layer sheets rolled up in a spiral structure with no internal aqueous phase between them. This technology was able to answer the challenges of oral delivery of different kind of biological molecules, especially the hydrophobic ones. Cochleates differ from liposomes in having water-free interior, rod-shaped, and rigid stable structure.

Basics of Cochleate and Nanocochleates

Cochleate and nanocochleates are novel lipid-based drug delivery system which represents a new approach suitable for the administration of a wide range of therapeutics including drugs, genes, and vaccine antigens. Then nanocochleate drug delivery vehicle is based on encapsulating the drug in a multilayered, lipid crystal matrix (a cochleate) to

potentially deliver the drug safely and effectively. Nanocochleates are cylindrical (cigar-like) microstructures that consist of series of lipid bilayers. Nanocochleate delivery vehicle are stable phospholipid-cation precipitates composed of simple naturally occurring material like polyphosphotidylserine and calcium. They have unique multilayered structure consisting of a solid, lipid bilayer sheet rolled up in a spiral or in a stacked sheet in order to minimize their interaction with water. They posses little or no aqueous internal space between them. The entire cochleate and nanocochleate structure is a series of solid layers so that, even if the outer layers of cochleate and nanocochleate are exposed to harsh environmental conditions or enzymes, the encapsulated drug molecules will be remain intact within the interior. Nanocochleates contains both hydrophilic and hydrophobic surface which makes it more suitable for encapsulation of both hydrophobic drugs like amphotericin B and clofazimine and amphipathic drugs like doxorubicin. It represents the most versatile technology for encapsulating drug within the interior of the nanocochleates structure. This nanocochleate structure remains intact, even though the outer layers of the nanocochleate may be exposed to harsh environmental conditions or enzymes.

Nowadays, oral route remains the alternative way for administrating therapeutic agents. In particular, lipid-based nanocochleate delivery system appears to provide answers to oral delivery challenges by formulating different kinds of biological molecules including genes, proteins and peptides and vaccines, antigens and drugs, especially hydrophobic once that were not having oral bioavailability. Nanocochleates are stable lipid-based delivery formulations whose structures and properties are very different from liposomes. Nanocochleates are unique platform technology for the delivery of with ranges of drugs and molecules such as proteins and peptides, polynucleotides. Thus, it is a potential drug delivery system for the wide class of drugs.

Components of Nano-cochleate Drug Delivery System

The three major components used in the preparation of nanocochleates are atmospheric pressure ionization (API), lipids, and cations.

1. Lipids: Phosphatidyl serine (PS), phosphatidic acid (PA), di-oleoyl PS, phosphatidylinositol (PI), phosphatidyl glycerol (PG), phosphatidyl choline (PC), di-myristoyl PS, phosphatidyl ethanolamine (PE), di-phosphatidyl glycerol (DPG), dioleoyl phosphatidic acid, di-stearoyl phosphatidyl serine, di-palmitoyl PG, etc.

2. Cations: Zn+2 or Ca+2 or Mg+2 or Ba+2, etc.

Advantages of Nanocochleates

1. Because of less oxidation of lipids and water free inner core, the nanocochleate are more stable than liposomes. Nanocochleates maintains the structure after lyophilization, whereas liposomes structures are destroyed by lyophilization. We can lyophilized cochleates to a powder.
2. Lyophilization is a potential method for storing formulations for longer duration of time at room temperature. Before administration of lyophilization, could be an advantageous method for transport and storage.
3. They exhibit the efficient incorporation of hydrophobic drugs into lipid bilayers of nanocochleate structure. They can also exhibit efficient incorporation of antigens with hydrophobic moieties into lipid bilayers of nanocochleate structure.
4. By formulating nanocochleate, intravenous drugs can be administered orally. For example, amphotericin B, a potent antifungal.
5. By encapsulating the drug, it reduces the stomach irritation and other side effects. They protect the encapsulated drug from degradation avoiding by exposure to adverse environmental conditions such as sunlight, oxygen, water, and temperature.
6. The components of lipid bilayer composed of simple lipids, that are naturally occurring and makes nanocochleates a safe and biocompatible delivery vehicles.
7. By encapsulating the drug, they improve the oral bioavailability of a broad spectrum of compounds, such as those with poor water solubility and proteins and peptides, biopharmaceuticals, which have been difficult to administer. For example, Ibuprofen for arthritis.
8. They are produced easily and safely.

3. Review of Literature and Development in the subject (Previous work done in the relevant area):

1. **S A Sonawane et al (2017)**

The researcher was prepared quercetin loaded nanocochleates to improve its therapeutic efficacy and cytotoxicity in human breast cancer cell line MCF-7. Quercetin-loaded nanocochleates was prepared by a trapping method. The optimized quercetin-loaded nanocochleates were evaluated for size, entrapment efficiency, in vitro quercetin release, cytotoxicity study.

Stable rolled-up layers as well as a tubular structure of nanocochleates possessing particle size and encapsulation efficiency of 180 ± 3 nm and 76.69 ± 3.21%, respectively were obtained. Nanocochleates demonstrated sustained release of quercetin at physiological pH. A significant improvement in vitro anticancer towards human breast cancer MCF-7 cells was observed.

2. **Beatriz et al (2017)**

In the present study, the essential oil from Artemisia absinthium L. (EO-Aa), Asteraceae formulated in nanocochleates (EO-Aa-NC) was investigated in vitro against intracellular amastigotes of L. amazonensis and non-infected macrophages from BALB/c mice. In addition, the EO-Aa-NC was also evaluated in vivo against on experimental cutaneous leishmaniasis, which body weight, lesion progression, and parasite load were determined.

EO-Aa-NC displayed IC 50values of 21.5±2.5µg/mL and 27.7±5.6µg/mL against intracellular amastigotes of L. amazonensis and non-infected peritoneal macrophage, respectively. In the animal model, the EO-Aa-NC (30 mg/kg/intralesional route/every 4 days 4 times) showed no deaths or weight loss greater than 10%. In parallel, the EO-Aa-NC suppressed the infection in the murine model by approximately 50%, which was statistically superior ($p < 0.05$) than controls and mice treated with EO-Aa. In comparison with Glucantime®, EO-Aa-NC inhibited the progression of infection as efficiently ($p > 0.05$) as administration of the reference drug.

3. **Akash Yadav et al (2016)**

The researcher studied that the formulation of nanocochleates of rifampicin is a promising and good strategy for improving its absorption through instestinal mucosa. It was

observed that the cochleate formulation of rifampicin shows significant increase in apparent permeability.

Permeability studies of the cochleate formulation of rifampicin shows more than two fold increase in the apparent permeability over normal rifampicin. The apparent permeability of rifampicin was found to be 3.56 × 10-6 cm/s. Formulation of drug as nanocochleates increased its absorption through the instestinal mucosa. This resulted in a significant increase in the apparent permeability to 7.78 ×10-6 cm/s. Hence the presented work proves a marked increase in permeability of rifampicin through small instestine by its formulation as nanocochleates, which is a good strategy to overcome the problem of malabsorption of rifampicin in presence of other anti-TB drugs as well as food and antacid, thus lowering the dose and side effects of the drug and requires further clinical studies to confirmation.

4. A P Pawar et al. (2014)

In this study the researcher were developed PTX-loaded nanocochleates (PTXNC) by addition of calcium ion into preformed nanoliposomes (PTXNL) comprising PTX, phosphatidylcholine and cholesterol and evaluated by in vitro and in vivo methods in comparison with PTXNL and pure PTX.

Based on the clinical fact that paclitaxel (PTX) intravenous injection frequently causes hypersensitive reaction, its oral administration is vital for its clinical development. However, the development oral PTX formulation is difficult due to its low oral bioavailability caused by its low permeability, low solubility, efflux and affinity for intestinal and liver metabolic enzymes. In an effort to develop an alternative formulation of PTX suitable for oral administration, PTX-loaded nanocochleates (PTXNC) were developed by addition of calcium ion into preformed nanoliposomes (PTXNL) comprising PTX, phosphatidylcholine and cholesterol and evaluated by in vitro and in vivo methods in comparison with PTXNL and pure PTX. Stable tubular rod structure of PTXNC possessing particle size, encapsulation efficiency and zeta potential of 269 _ 2 nm, 71.12 _ 1.87% and _3.9 mV, respectively were obtained from homogenous unilamellar, discrete and spherical structured nanoliposomes with diameter and zeta potential of 247 _ 3 nm and _12.3 mV, respectively. Powder X-ray diffraction and thermal study revealed that PTX was partial crystalline and amorphous state in PTXNL and PTXNC, respectively. PTXNC demonstrated controlled release of PTX. PTXNC showed many fold improvement in vitro anticancer activity towards A-549 (human lung

adenocarcinoma cells), ovarian cancer OVCAR-3 and breast cancer MCF-7 cells with a 14- and 19-fold increase in oral bioavailability in rats as compared to PTXNL and pure PTX, respectively. Moreover, PTXNC showed low tissue distribution. These results collectively suggest that nanocochleates could therefore advantageously be employed to improve anticancer activity of PTX and an alternative to the present intravenous administration.

5. **Bothiraja et al (2013)**

In present study researcher were developed and evaluated fisetin-loaded nanocochleates to improve its therapeutic efficacy. Using the trapping method, fisetin-loaded dimyristoylphosphatidylcholine liposomal vesicles were converted into nanocochleates by the action of Ca2+ ions. These nanocochleates were further evaluated for physicochemical, in vitro anticancer and haemolysis, pharmacokinetics and tissue distribution study in mice.

Stable rolled-up layers as well as elongated structure of nanocochleates possessing particle size and encapsulation efficiency (EE) of 275 + 4 nm and 84.31 ± 2.52%, respectively were obtained. Nanocochleates demonstrated safety and a sustained release of fisetin at physiological pH. A 1.3-fold improvement in vitro anticancer towards human breast cancer MCF-7 cells was observed. Pharmacokinetics studies in mice revealed that nanocochleates injected intraperitonially showed a 141-fold higher relative bioavailability. Moreover, a low tissue distribution was observed.

6. **Pawar et al (2013)**

Present study involved the development and evaluation of phosphatidylserine based cochleate formulation of ketoconazole, the model drug of the study. A 32 factorial design was utilized to optimize cochleate formulation and to study effect of phosphatidylserine and drug on the properties and performance of cochleates. Cochleates were also characterized by FTIR and DSC. The antifungal activity and stability of KCZ cochleates too was investigated.

Cochleates of size 0.282 µm ± 0.05 to 72.52 µm ± 2.2 and entrapment efficiency of 57.86% ± 4.55% to 97.27% ± 2.77 were obtained. The variables of the 32 factorial design significantly affected the cochleate size. Cochleates demonstrated promising role in topical delivery of drugs as the small sized cochleates caused significant release across the skin while the larger ones were retained in the skin leading to drug accumulation therein. Antifungal activity testing confirmed the preservation of antifungal activity by the encochleated drug.

Nevertheless, the prepared cochleate formulations possessed stability profile similar to liposomal counterpart.

7. **Santangelo et al (2000)**

The researcher prepared cochleates containing Amphotericin B (CAMB) inhibit the growth of Candida albicans, and the in vivo therapeutic efficacy of CAMB administered orally was evaluated in a mouse model of systemic candidiasis. The results indicate that 100% of the mice treated at all CAMB doses, including a low dosage of 0.5 mg/kg of body weight/day, survived the experimental period (16 days). In contrast, 100% mortality was observed with untreated mice by day 12. The fungal tissue burden in kidneys and lungs was assessed in parallel, and a dose-dependent reduction in C. albicans from the kidneys was observed, with a maximum 3.5-log reduction in total cell counts at 2.5 mg/kg/day. However, complete clearance of the organism from the lungs, resulting in more than a 4-log reduction, was observed at the same dose. These results were comparable to a deoxycholate AMB formulation administered intraperitoneally at 2 mg/kg/day ($P < 0.05$). Overall, these data demonstrate that cochleates are an effective oral delivery system for AMB in a model of systemic candidiasis.

4. Objectives of Research/ Proposed Hypothesis:

Aim: Formulation, Development and Evaluation of Nanoparticulate Drug Delivery System for Anticancer drug.

Objectives of the Research Work:

- To formulate, optimize and characterize anticancer drug-loaded nanocochleates.
- To improve the efficacy, drug loading capacity and biocompatibility of anticancer drug by formulating in nanocochleates.
- To minimize the toxicity and increase the stability of anticancer drug by encapsulating in nanocochleates system.
- To evaluate anticancer potential of formulation by in-vitro cell culture study.
- To evaluate in-vivo bioavailability of drug from formulation in comparison with pure drug in experimental animal.
- To study the tissue distribution of drug from formulation in comparison with pure drug in experimental animal.

5. Materials and Methodology to be adopted:

1. **Literature review**
2. **Selection and Collection of anticancer drug & excipients**

   Selection of anticancer drug: e.g. Etoposide or Gemcitabine or Docetaxel etc.

   Selection of a lipid: To formulate the nanocochleates, one of the following lipid will be selected e.g. Phosphatidylserine or Phosphotidylethanolamine or Phosphotidylcholine or Phosphatidylinosotol etc.
3. **Experimental work**
   - **A. Characterization of drug and excipients**
     1. **Spectroscopic studies**
     2. **Solubility studies**
     3. **Crystallinity studies**
   - **B. Compatibity studies**
4. **Formulation development**
   - Preparation of Nanocochleates

   Step I: Preparation of drug loaded nanoliposomes

   Liposomes will be prepared by ethanol injection method or rotary evaporator method or any other suitable method

   Step II: Preparation of drug loaded nanocochleates

   Nanochleates of above prepared nanoliposomes will be prepared by trapping method or any other suitable method.
   - Optimization and lyophilization of drug-loaded nanocochleates
5. **Characterization of drug-loaded Nanocochleates**
   - Yield and drug content
   - Particle size and zeta potential
   - Encapsulation efficiency
   - Surface morphology by Transmission electron microscopy (TEM)
   - Fourier transform infrared spectroscopy
   - PXRD study
   - Differential scanning colorimetry
   - In vitro drug release

6. **In vitro anticancer cell line study**
7. **In vivo pharmacokinetic study**
8. **Stability studies.**

6. Importance of study/ Society application:

- **International status:** Nanotechnology is a rapidly evolving domain, as it answers to various issues associated with conventional drug delivery. This is very true in diseases like cancer where there are many challenges. Worldwide there is increasing number of cancer patients, consequently anticancer drug use also increased. Most of the studies in last few years with nanoparticulates showed a promising result and accordingly there is increasing number of patents on nano drug delivery in chemotherapy of cancer.
- **National status:** Being a second largest populated country in the world, India is facing a many more challenges in cancer therapy. Increased number of cancer patients in India due to smoking, sedentary life style, poor living standard, pollution, lack of awareness on cancers early signs and symptoms etc. A big issue in India is lack of availability of most effective, safe and economic drug delivery for cancer chemotherapy. Nanoparticulates, especially nanocochleates have the potential to overcome the challenges related to cancer chemotherapy. There is huge scope in India to develop a drug delivery with improved efficacy, biocompatibility, biodistribution and minimized toxicity in cancer chemotherapy.

►Significance of the study:

At present anticancer drug therapy has many challenges like drug resistance, lack of selectivity, lack of drug solubility, dynamic changes of cancer cells, serious side effects of chemotherapy, poor targeting of heterogenic tumors, small amount of drug reaches the cancer cell, inability of the drug to enter the core of the tumors, resulting in impaired treatment with reduced dose and survival rate etc. In reference to these challenges, it becomes necessary to formulate a novel drug delivery system which is promising, more effective and safe.

One of the nanoparticulate drug delivery system is the lipid based nanocochleates system which bears potential for the development of innovative pharmaceuticals due to its many advantages such as biocompatibility, increased drug loading capacity, ease and safety of production, reduced side effects and improved efficacy. In recent studies nanocochleates loaded with anticancer drug showed improved bioavailability, biocompatibility, efficacy, drug loading capacity and decreased toxicity. Hence it is need of hour to develop a formulation of the anticancer drugs in nanocochleate system.

7. Proposed work Plan/ Formulation and Structure of Study:

Year-wise Plan of work and targets to be achieved:

Sr. No.	**Expected target to be achieved**	**1-6 months**	**7-10 months**	**11-22 months**	**22--27 months**	**28- 33 months**	**34-36 Month**
01	Literature survey	Literature survey					
02	Selection and collection of drug and excipients	Selection and collection of drug and excipients					
03	Formulation, development and optimization	Formulation, development and optimization					
04	Evaluation of nanocochleates	Evaluation of nanocochleates					
05	In vitro and in vivo study	In vitro and in vivo study					
06	Statistical Analysis, Data Interpretation and Conclusions	Statistical Analysis, Data Interpretation and Conclusions					
07	Publishing Research and submitting data	Publishing Research and submitting data					

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